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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/802,644	03/17/2004	Linda D. Martin	5051-574CT	3963

20792 7590 06/29/2005

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/802,644	MARTIN ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,8-14,20-27 and 49-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 8-14, 20-27, 49-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.00

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 4/18/05, is acknowledged.

2. Claims 1-4, 8-14, 20-27 and 49-51 are pending and under examination.

3. In view of the amendment filed on 4/18/05, only the following rejections are remained.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-4, 8-14, 20-27 and 49-51 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons set forth in the previous Office Action mailed 11/30/04.

Applicant's arguments, filed 4/18/05, have been fully considered, but have not been found convincing.

Applicant asserts that the specification enables the claimed invention. Applicant directs the examiner's attention to Fig. 9, Fig. 10, paragraph 49, figures 11-15, and Figs 3A-3C to illustrate that the enablement standard is satisfied in the present application. Further Applicant points to paragraph 16 of the specification to illustrates that the specification provides guidance to one of skill in the art to make active fragments of SEQ ID NO: 1.

However, the specification does not provide a sufficient enabling description of the claimed invention. The specification discloses only a single MANS peptide of sequence (SEQ ID NO:1) with a disclosed activity of blocking mucin secretion through PKC/PKG dependent signaling in NHBE cells (e.g., page 16, 65¶). The instant claims encompass in their breadth *any* MANS peptide fragment, any compound that "inhibits the MARCKS-related release of inflammatory mediators" or regulates mucin granule release; or *any* inflammatory mediator, any antibibotic, any antiviral compound, any antiparasitc compound any anti-inflammatory compound any immunosuppressant, or any inflammation, any cellular secretory process including those that comprise "infiltrating inflammatory cells".

Besides SEQ ID NO: 1, there does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the various MARKS/ fragments, or any compound that inhibits MARCKS-related release of inflammatory mediators or regulates mucin granule release recited in the instant claims. A person of skill in the art would not know which

MARCKS/MANS fragments or which compounds are essential, which peptides and compounds are non-essential, and what particular sequence lengths identify essential sequences "at least six amino acids in length". Besides, SEQ ID NO: 1, there is insufficient guidance to direct a person of skill in the art to select particular peptides or peptide lengths as essential for the suppression of mucin secretion dependent signaling. Without detailed direction as to which peptide sequences are essential to the function of MANS peptide of SEQ ID NO:1, a person of skill in the art would not be able to determine without undue experimentation which of the plethora of compounds that inhibits the MARCKS-related release of inflammatory mediators, or active fragments of a MARKS protein encompassed by the instant claims would share the ability to inhibit mucin secretion dependent signaling other than SEQ ID NO:1.

Beside SEQ ID NO:1, the specification is silent with respect to specifically which "compound", "MANS fragment" or "MARKS protein fragment" which are critical to the claimed inhibition of the release of mucin granule function such that one skilled in the art could predict which species would fall within the scope of the claims to be used in the method of inhibiting mucus secretion for the claimed diseases.

The instant claim language appears to encompass subsequences. For example, claims 1-2 recite fragments of SEQ ID NO: 1 and claim 25-26 recite an active fragment of MARCKS protein comprises at least six amino acids. Such a recitation does not require that the full length sequence set forth in SEQ ID NO:1; but rather encompasses any amino acid sequence comprising either the full length of SEQ ID NO:1or MARKS protein or *any subsequence thereof*. However, the specification does not appear to have provided sufficient guidance as to which subsequences of SEQ ID NO:1/MARKS would share the function of inhibiting mucin secretion dependent signaling. Neither does the specification appear to have provided any working examples of any functional subsequences. Thus it would require undue experimentation of the skilled artisan to determine which subsequences of SEQ ID NO:1 would have the function of the full length molecule.

Applicant submits that one of skill in the art would be able to readily predict the ability to modulate neutophils, basophils, eosinophils, monocytes or leukocytes. Applicant notes that an enhanced secretory response to PMA alone was documented in NHBE cells (Fig.1 column 4) and in neutrophils (Fig. 11). Further Applicant submits that blocking antibodies have been demonstrated as useful therapies against inflammation in the neutrophil associated tissue injury in acute inflammation (Harda et al 1996, Molecular Medicine Today 2, 482).

However, while the specification provides some guidance with respect to neutrophils, claims 49-51 recite the reducing/inhibiting an inflammatory mediator, however there are no working examples in the specification to modulate any neutrophils, basophils, eosinophils, monocytes or leukocytes. There is no evidence of record that demonstrates that the MANS peptide would function to modulate those inflammatory mediators. The lack of any working examples is exacerbated because the invention is in a highly unpredictable art-regulating the airway mucus

hypersecretion-and while the level of skill of a practitioner in the art may be high, the state of the prior art is that it is in fact unknown and untested what are the underlying inflammatory mediators and the physiologic bases of the therapeutic effects of MANS peptide in the treatment of inflammation. Regarding Harada et al, since the Applicant has did not provide the reference, the examiner, only can comment on the abstract which is available PubMed. Harada et al do not disclose any method to inhibit an inflammatory mediator in a subject, but rather used anti-IL8 antibody to alleviate acute inflammation. Claimed invention uses MANS/ MARCKS peptide/protein to inhibit an inflammatory mediator in a subject.

With respect to the in vivo therapeutic methods, Applicant further submits that the in vitro data can be readily extrapolated to the in vivo methods claimed. Applicant presents examples disclosed in the specification that relate to mucin secretion. Applicant points to M.P.E.P., "compliance with the enablement requirement of 35 U.S.C. 1 12, first paragraph, does not turn on whether an example is disclosed." M.P.E.P. 2164.02. Moreover, M.P.E.P. 2164.02 further states that "because only an enabling disclosure is required, applicant need not describe all actual embodiments." With respect to Applicants presentation of in vitro data, Applicants submit that one of ordinary skill in the art is provided enough information in the form of in vitro data to determine an in vivo method of treating inflammation in a subject, comprising administering an effective amount of a MANS peptide to a subject in need of such treatment. Applicant notes that the normal human bronchial epithelial cell type and the nature of the experiments conducted are particularly suited for correlation of results obtained in vitro to results expected from in vivo experiments. Applicant concludes that the observed effects on the epithelial cells in vitro provide one of ordinary skill in the art the tools to conduct routine experimentation to devise a treatment protocol for a subject in need of treatment as provided by the present application. Applicant notes that if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless there is evidence that the model does not correlate.

However, the scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims." MPEP § 2164.03. Further, if the use disclosed is of such nature that the art is unaware of successful treatments with chemically analogous compounds, a more complete statement of how to use must be supplied.

Although Applicant's specification describes certain in vitro experiments, there is no correlation on this record between in vitro experiments and a practical in vivo use in currently available form for humans or animals. It is not enough to rely on in vitro studies where, as here, a person having ordinary skill in the art has no basis for perceiving those studies as constituting recognized screening procedures with clear relevance to use in humans or animals (emphasis added). Ex parte Maas, 9 USPQ2d 1746. Substantiating evidence may be in the form of animal

tests which constitute recognized screening procedures with clear relevance to use in humans. See Ex parte Krepelka, 231 USPQ 746 (Board of Patent Appeals and Interferences 1986) and cases cited therein. Ex parte Maas, 9 USPQ2d 1746. There must be a rigorous correlation of pharmacological activity between the disclosed in vitro use and an in vivo use to establish practical use.

6. Claims 1-4, 8-14, 20-27 and 49-51 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action mailed 11/30/04.

Applicant's arguments, filed 4/18/05, have been fully considered, but have not been found convincing.

Applicant submits that the claims have been amended to recite "active fragment of the MANS peptide comprises at least six amino acids" to include the recitation "wherein said active fragment inhibits an inflammatory mediator". Applicant submits that one of skill in the art could readily draw up a list of six amino acids from the MANS peptide and prepare an assay to test the activity of each fragment.

However, just because a broad genus claim is amended to include a functional limitation does not, by default, necessarily mean the written description rejection should fall. Since there is no information regarding domains or regions that are responsible for the claimed function, very little is known about the peptide of SEQ ID NO: 1, and only SEQ ID NO:1 fragment species is disclosed.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-4, 8-14, 20-27 and 49-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adler et al (CHEST. May, 2000, of record), as is evidenced by the specification on page 26, lines 11-15 for the same reasons set forth in the previous Office Action mailed 11/30/04.

Applicant's arguments, filed 4/18/05, have been fully considered, but have not been found convincing.

Applicant argues in conjunction with case law that the present invention relates to methods of inhibiting **inflammatory mediators released from inflammatory cells** and not **epithelial cells** as recited in Adler (emphasis added by Applicant). Applicant submits that it is well known in the art that **epithelial cells and inflammatory mediators are different** from one another. Applicants submit that it is known that a wide variety of agents and inflammatory/humoral mediators can provoke mucin secretion. These include cholinergic agonist, lipid mediators, oxidants, cytokines, neuropeptides, ATP and UTP, bacterial products, neutrophils elastase, and inhaled pollutants. Further Applicant notes that epithelial cells and inflammatory cells have very different responses to exogenous stimuli and can have different biochemical signaling pathways. Applicant concludes that it would not be expected from this publication that inflammatory cells would behave similarly to epithelial cells. Applicant further submits that Adler does not teach or suggest the present invention. Applicant submits that nothing in the reference would make the present invention obvious. Applicant submits that this reference fail to contain any motivation to combine their teachings as required by in re Sang-su Lee.

However, Appellant does provide objective evidence to distinguish the prior art from the claimed invention. Given that hypersecreation of mucus contributes to air way inflammation and obstruction in COPD and that MARCKS protein is a major cellular substrate for protein kinase C, is a central, convergent intracellular molecule controlling release of mucine granules by airway goblet cells, it would have been obvious to one of ordinary skill in the art at the time the invention was made to consider practice the method taught by Adler et al in mammalian subject including humans. The recitation "block the release of mediators of inflammation secreted from infiltrating inflammatory cells" would be an expected property of the obvious method.

9. Claim 51 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Adler et al (CHEST. May, 2000, of record), as is evidenced by the specification on page 26, lines 11-15, as applied to claims1-4, 8-14, 20-27 and 49-50 above, and further in view of U.S Patent No. 6,506,779 of record for the same reasons set forth in the previous Office Action mailed 11/30/04.

Applicant's arguments, filed 4/18/05, have been fully considered, but have not been found convincing.

Applicant submits that the '779 patent does not in any way discuss or even contemplate the MANS peptide or a MARCKS related protein. Applicant concludes that the '779 patent and Adler either alone or in combination fail to contain any motivation to combine their teachings as required by in re *Sang-Su Lee.*

However, "it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205USPQ 1069, 1072 (CCPA 1980) (see MPEP 2144.06).

10. No claim is allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher Haddad, Ph.D.
Patent Examiner
June 20, 2005

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